REMARKS

Status of the Claims

Claims 1-39 are pending in this application.

Claims 1-39, currently under examination, stand rejected.

Claims 1, 3, 4, 16, 31, and 32 are amended herein. No new matter is introduced.

Claim Amendments

Claims 1, 3, 16, and 31 are amended herein to specify the treatment of "unwanted pigmentation associated with production of melanin." This language is supported by the application as filed, and in particular, at pages 4-5, paragraph [0020] and at page 7, paragraph [0038]. For example, see paragraph [0020] on page 5: "...the siRNA oligomers block or inhibit native human tyrosinase, which in turn, results in an inhibition of tyrosinase enzyme production and a reduction of pigmentation because the tyrosinase enzyme will not be present for melanin synthesis."

Claims 4 and 32 are amended herein to remove duplicate sequences, consistent with the amendment filed on June 2, 2006. This amendment was entered by the Examiner, and in the response of May 30, 2007, the amended portions were inadvertently left out of the claim listing by Applicants. The present amendment corrects this mistake, restoring claims 4 and 32 to their form as amended on June 2, 2006.

Claim Rejections

35 U.S.C. §112, first paragraph: enablement

The Examiner has maintained the rejection of claims 1-39 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. Briefly, the Examiner contends that the instant application lacks enablement because (1) as a technology, siRNA delivery is unpredictable, and (2) the claims are not commensurate with the scope of enablement provided by the instant application. Applicants traverse this rejection for the following reasons.

The unpredictability associated with in vivo delivery of siRNA alleged by the Examiner does not reflect the state of the art as of Applicants' filing date. The Examiner relies on Caplen et al., 2000 ("Caplen 2000") and Caplen 2003 ("Caplen 2003") to support the alleged

unpredictability associated with the use of siRNA. In the Office Actions of October 18, 2005 and March 30, 2007, the Examiner relied on Caplen 2000 as support for the unpredictability of siRNA delivery in vitro by pointing out one example in 293 cells and one in BHK1 cells, in which there was no effect, or non-specific reductions in gene expression after using dsRNA. Applicants submit, however, that Caplen 2000 has little or no relevance to the enablement of the present claims, as it was published three years prior to the filing date of the present application and thus does not reflect the state of the art at the time the instant application was filed.

RNA interference was a rapidly evolving art at the time of Caplen 2000, and by the filing date of the instant application (December 2003), the successful delivery and use both in vitro and in vivo of siRNA was routine, as evidenced by Caplen 2003. Caplen 2003 states, "[s]ince the publication of these first papers, numerous studies have reported utilization of RNAi knockdown in mammalian cells," and one of the "first papers" to which the author refers is Caplen 2000. Thus, Caplen 2003 underscores the fact that Caplen 2000 does not reflect the state of the art at the time the application was filed.

Caplen 2003 reviews the state of the literature three years after Caplen 2000, and in doing so cites numerous studies in which the in vitro use of RNAi is successful, (see, e.g., page 578, for a discussion of the success of RNAi in cancer cells). The Examiner relies on Caplen 2003 to support the assertion that the in vivo delivery of siRNA "remains a challenge that needs to be addressed" (Office Action, page 5) and that "[m]any of the problems associated with developing RNAi as an effective therapeutic are the same as those encountered with previous gene therapy approaches" (October 18, 2005 Office Action). These generalized statements do not negate the substance of the article which discusses the vast strides that RNA interference has made as a technology and the numerous instances in which RNA interference has been used successfully in vivo. For example, Caplen 2003 describes the success in using high-pressure tail vein injections into mice for delivery of siRNA, as well as the successes in using an adenoviral vector for delivery, and in generating transgenic mice from embryonic stem cells expressing siRNA (Caplen 2003, page 580). In fact, **there is not a single example in Caplen 2003 which describes a failure of siRNA in vivo**.

Applicants also direct the Examiner's attention to the review article, "Progress Towards in Vivo Use of siRNAs" (M.A. Behlke, Progress towards in vivo use of siRNAs, Mol.

Ther., 13(4): 644-670, 2006), which documents the success of siRNA in vivo through a discussion of the more than 90 publications which describe the successful use of RNA interference in vivo, spanning the years 2002-2006. Importantly, many successful studies of in vivo siRNA cited by Behlke include topical administration. As an example, one referenced paper demonstrates successfully administered siRNA in a murine deafness model system, delivering the siRNA to the cochleae of mice in DOTAP/cholesterol liposomes. (Y. Maeda at el., In vitro and in vivo suppression of GJB2 expression by RNA interference, Hum. Mol. Gen., 14(12), 1641-1650, 2005). Applicants point out that delivery through liposomes is described as a suitable delivery vehicle in the instant invention, supported by the specification at page 12, paragraph [0051]: "Accordingly, such liposomes can be formulated into any of the dermatological or cosmetic compositions as described herein." The Examiner's attention is directed to yet another example of successful topical delivery of siRNA, published by D. Palliser et al., in which siRNA was delivered in a lipid carrier and applied intravaginally (to the epithelial surface) to block HSV2 infection in mice. ("An siRNA-based microbicide protects mice from lethal herpes simplex virus 2 infection," Nature, 439(5): 89-94, 2006). In both of the above publications, the effects were described as specific to the RNA interference, and did not cause immune stimulation. Applicants also point out that the successful in vivo results described correlated with the success that these authors showed in cell lines, within the same publications.

Behlke cites numerous other instances of success with siRNA in vivo, with publication dates prior to or contemporaneous with the filing date of the instant application. For example, Lewis et al. (2002) provides data for successful delivery of siRNA in several different organs in a mouse model, S. Filleur et al. (2003) demonstrates successful siRNA delivery against fibrosarcoma tumor cells in mice, and Reich et al. (2003) demonstrates successful siRNA delivery against EGFP in the eye, in a mouse model.[1] Dozens of other such examples of the successful use of siRNA are documented in Behlke 2006, and provide ample evidence that the use of siRNA in vivo is not generally unpredictable, as the Examiner suggests. In fact, Applicants question the Examiner's conclusion regarding the unpredictability of the use siRNA,

[1] D.L. Lewis et al., Efficient delivery of siRNA for inhibition of gene expression in postnatal mice, Nature Gen., 32: 107-108; S. Filleur et al., SiRNA-mediated inhibition of vascular endothelial growth factor severely limits tumor resistance to antiangiogenic thrombospondin-1 and slows tumor vascularization and growth, Cancer Res., 63: 391903922, 2003; S.J. Reich et al., Small interfering RNA (siRNA) targeting VEGF effectively inhibits ocular neovascularization in a mouse model, Mol. Vision, 9: 210-216.

when none of the art of record demonstrates it as such, except for one in vitro study cited by the Examiner in Caplen 2000, a paper published three years before the filing date of the instant application, and which the author herself describes as outdated in a later paper (Caplen 2003).

The Examiner also refers to Zhang et al. (2004, of record), to comment that "effective delivery of siRNAs to mammalian cells will not be so simple." In fact, after the quote in Zhang that the Examiner cites, Zhang goes on to describe the effective delivery of siRNA to the liver by high pressure tail-vein injections: "...delivery of siRNA to the liver by high-pressure tail-vein injections results in uptake of siRNA by at least a majority of hepatocytes." (page 5). Zhang cites no instance of a failure of the technology. Applicants submit that the ambiguous statement that siRNA delivery will "not be so simple" has no bearing on the enablement of the present claims, particularly in view of the fact that the use of siRNA in Zhang was successful. Whether or not a technology is "simple" is not the standard for assessing whether undue experimentation would have been required.

There are also many examples of successful topical delivery of oligonucleotides, in general, with publication dates prior to the filing date of the instant application. For example, as early as 2000, C.J. Wraight et al. demonstrated that topically administered oligonucleotides penetrate the epidermis of human skin when grafted onto mice. ("Reversal of epidermal hyperproliferation in psoriasis by insulin-like growth factor I receptor antisense oligonucleotides," Nature Biotech., 18: 521-526, 2000). Also in 2000, R.C. Mehta et al. demonstrated successful topical delivery of oligonucleotides to inhibit TNF-α expression in human skin grafted onto mice. (Intercellular adhesion molecule-1 suppression in skin by topical delivery of anti-sense oligonucleotides, J. Invest. Derm., 115:805-812, 2000).

The Examiner also maintains that the treatment of skin disorders in unpredictable, citing "Hartmann et al. (2004) to indicate that the "pathophysiology of hypopigmentary disorders is still poorly understood." (Office Action, October 18, 2005 and reiterated in Office Action of July 10, 2007). The Examiner contends that the "other unwanted pigmentation" of the instant claims encompasses hypopigmentation. The instant invention, however, is not directed to hypopigmentary disorders, but rather is directed to disorders related to the production of melanin (as opposed to the lack thereof), which leads to hyperpigmentation, or unwanted pigmentation. Specifically, see paragraph [0020] on page 5: "...the siRNA oligomers block or inhibit native

human tyrosinase, which in turn, results in an inhibition of tyrosinase enzyme production and a reduction of pigmentation because the tyrosinase enzyme will not be present for melanin synthesis." Applicants disagree that the "unwanted pigmentation" of the instant claims encompasses hypopigmentation, but to advance prosecution, applicants have amended claims 1, 3, 16, and 31 to recite "...or other unwanted pigmentation associated with production of melanin."

In view of at least the foregoing, Applicants submit that the instant claims fully comply with the enablement requirement of 35 U.S.C. §112, first paragraph, and respectfully request withdrawal of all rejections.

35 U.S.C. §112, first paragraph: written description

The Examiner has rejected claims 1-3 and 5-31 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner states that "the human and mouse mRNA sequences have not been defined by applicant in a way that would allow for one of ordinary skill in the art to envision which siRNA oligomers are directed to both sequences without further knowledge of the sequences." Applicants traverse the rejection.

The sequences for both human and mouse tyrosinase have been known in the art for many years, well before the filing date of the instant application (see GenBank sequence identification no. gi:340039 for human tyrosinase, 1995 and no. gi:202249 for mouse tyrosinase, 1993). Therefore, the knowledge of these sequences, which is necessary according to the Examiner, was readily available to one of ordinary skill in the art. Because these nucleotide sequences were known in the art at the time of filing of the instant application, Applicants are not required to reproduce them in the application. see Falko-Gunter Falkner v. Inglis, 448 F.3d 1357 (Fed. Cir. 2006) (holding that where "accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences . . . satisfaction of the written description requirement does not require either the recitation or incorporation by reference . . . of such genes and sequences.") As noted by the Examiner, Applicants have provided several examples in the instant application of sequences that are homologous to both mouse and human tyrosinase. In view of these representative sequences and the fact that the sequences of mouse and human mRNA were known, one of ordinary skill in the art would have understood that Applicants were

in possession of all siRNA oligomers directed to both the human and mouse sequences. In view of at least the foregoing, Applicants respectfully request withdrawal of the written description rejection.

35 U.S.C. §102(e) and 35 U.S.C. §103(a)

The Examiner has rejected claims 1-3, 5-9, 14-25, and 31 under 35 U.S.C. §102(e) as being anticipated by Bennett et al. (US 2004/0215006). The Examiner has also rejected claims 1-3 and 5-31 under 35 U.S.C. §103(a) as unpatentable over Bennett et al. in view of Mahashabde et al. (US 6,436,378) and Perricone (US 2002/0141956). The Examiner states that Bennett teaches methods of modulating the expression of tyrosinase in cells, tissues, or animals, and that the compounds of Bennett can be single or double stranded antisense oligonucleotides. The Examiner further states that "Bennett et al. specifically teach oligomers that target human or mouse tyrosinase mRNA and are therefore necessarily considered to teach oligomers that would target both." (Office Action, page 10). Applicants traverse the rejection.

Bennett et al. discloses oligomers that target human tyrosinase mRNA. Bennett et al. also disclose oligomers that target mouse tyrosinase mRNA. However, these sets of oligomers are distinct, with some targeting human mRNA, and some targeting mouse mRNA. This is clearly demonstrated by the two separate tables provided listing the sequences separately; Table 1 provides oligomers for human tyrosinase mRNA and Table 2 provides oligomers for mouse tyrosinase mRNA. There is no indication in Bennett that any of the disclosed oligomers can be used interchangeably, or that any of the disclosed oligomers could be used to target both mouse and human mRNA. The instant claims recite "siRNA oligomers specific for mouse and human tyrosinase mRNA," and are therefore not anticipated by Bennett.

Regarding Mahashabde and Perricone, neither of these references either teaches or suggests the use of siRNA oligomers for treating hyperpigmentation or other unwanted pigmentation, or for improving the aesthetic appearance of the skin as recited in the instant claims and that therefore do not rectify the deficiencies of Bennett et al. Therefore, Applicants submit that the rejections under 35 U.S.C. §102(e) and 35 U.S.C. §103(a) should be withdrawn.

CONCLUSION

Based on the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application.

Respectfully submitted,

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